Clinical Predictors of Streptomycin-Vestibulotoxicity

Miraj Ahmed¹ · Anupam Mishra¹ · Kamal Kumar Sawlani² · Veerendra Verma¹ ·
Rajiv Garg³ · Hitendra Prakash Singh¹ · Sunil Kumar¹

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Abstract The Global tuberculosis control is challenged with a growing resistance to antitubercular treatment (ATT) culminating in resistant (MDR/XDR) strains; an important factor being premature withdrawal of streptomycin owing to its morbidity particularly nephrotoxicity and cochleotoxicity as guidelines for their prevention exist. An attempt is made here to address the least recognized and most debilitating vestibular toxic effects of streptomycin and defining a vestibular-protocol for its early detection

The current study was a part of the thesis work carried out by Dr Miraj Ahmad for Masters in Otorhinolaryngology under chief supervision or the corresponding author (Anupam Mishra).

✉ Anupam Mishra
anupampenn@yahoo.com
Miraj Ahmed
merajahmad2011@gmail.com
Kamal Kumar Sawlani
kksawlani@gmail.com
Veerendra Verma
drveerendraverma@rediffmail.com
Rajiv Garg
rajivkgmc@gmail.com
Hitendra Prakash Singh
drhpsingh77@gmail.com
Sunil Kumar
drsunil_kumar123@rediffmail.com

and progression. Thirty two prospective patients (treatment-failures, relapse and default cases) undergoing ATT (24 shots of IM streptomycin 15–20 mg/kg over 8 weeks) underwent complete vestibular workup including vestibulo-ocular and vestibulo-spinal reflex assessment with an attempt to closely follow them. Four categories (I: No-, II: Occult-, III: Delayed-Manifest- and IV: Manifest-vestibulotoxicity) were defined. The DHI and casual gait abnormality clearly differentiated III/IV from I/II. The occilopsia and head thrust tests significantly differentiated II from I. Rotation and bithermal calorics significantly differentiated I from II and II from III/IV. The Fukuda, Rhomberg, Tandem-Rhomberg and CTSIB were significant in differentiating I from II and II from III/IV. Dix-Hallpike and Positional tests were of no significance in the entire study. The Occilopsia and Head-Thrust tests that showed 100 % positivity for II to IV are more likely to better predict ‘manifest’ or ‘occult’ -vestibulotoxicity while DHI and casual gait assessment may be carried out by a paramedic at a peripheral center to suspect vestibulotoxicity. Since we found absolute compliance with our series we feel that vestibulotoxicity may not be a deciding factor for termination of streptomycin provided an in-built mechanism for patient support/counseling be incorporated in management schedule.

Keywords Vestibulotoxicity · Streptomycin · Tuberculosis

- ¹ Departments of Otolaryngology and Head and Neck Surgery, King George Medical University, Shahmeena Road, Lucknow, India
- ² Departments of Internal Medicine, King George Medical University, Lucknow, India
- ³ Departments of Pulmonary Medicine, King George Medical University, Lucknow, India

India has the largest burden of tuberculosis (TB) patients across the globe and despite the ongoing vigorous efforts of Revised National Tuberculosis Control Program (RNTCP)/WHO, the growing resistance to antitubercular treatment (ATT) is alarming. The latest trends revealing air-borne

transmission in one of every three general population is not surprising considering the erratic institution of ATT. Despite considerable progress through ‘DOTS’ program involving free available of drugs, there are still reported dropouts contributing to emerging resistance. Important determinants for dropouts include the adverse effects of aminoglycosides leading to premature withdrawal. Most physicians are familiar with the nephrotoxic and cochleotoxic side-effects and follow established guidelines for prevention. However the least recognized and most debilitating are the vestibular toxic effects. The detection still remains a challenge as there is no vestibular monitoring protocol with documented efficacy, reliability and suitability for such patients [1]. Hence to enhance the patient-compliance of ATT, it is essential to identify such debility in its early stages and manage accordingly.

Although the incidence of aminoglycoside-induced-vestibulotoxicity (AIV) has been estimated as 3–6 %, the true incidence is unknown because most studies have focused on renal and cochleotoxic effects [2, 3]. The threshold at which AIV precipitates is less predictable with much variation, so difficult to predict [4]. Moreover many individuals with partial hearing loss may compensate so that vestibular dysfunction is not suspected and formal vestibular assessment not considered. It is possible that AIV may start with the onset of treatment and the pattern of vestibular involvement may further define physical manifestations. Since the preferential involvement of ‘frequency-distribution’ of AIV-dysfunction is not known, it is difficult to predict the corresponding impairment. For example no-nystagmus on caloric testing often misinterpreted as a dead labyrinth actually signifies lower-frequency-vestibular-dysfunction only. Hence it is necessary to establish (1) AIV on entire ‘frequency range’ (2) criteria for identifying occult-AIV and (3) potential ‘manifest-AIV’. Hence in an attempt to establish the protocol for AIV assessment, we aim to shortlist the individual test or a combination of clinical tests/investigations that are likely to detect/predict the future course of AIV.

Materials and Methods

This is a prospective study on 32 patients of pulmonary TB (treatment-failures, relapse and default cases) undergoing ATT including injectable streptomycin. Table 1 depicts the inclusion and exclusion criteria while Table 2 defines the 4 clinical categories of vestibulotoxicities in our study.

These patients were initially dealt as per DOTS protocol and were referred for vestibular workup at the time of starting ATT but many attended by themselves with the onset of dizziness. These patients underwent Dizziness-Handicap-Inventory (DHI) (a 25-item questionnaire with

score ranging between 0 and 100 and a change of 18 points in total score being suggestive of a significant change). Two clinical screening tests were undertaken: (A) Head-Shake nystagmus with Frenzel glasses was elicited as per standard protocol [5] where objective nystagmus was observed. (B) Casual-gait with and without reciprocal horizontal head movements’ was undertaken with its result categorized as (1) normal or (2) abnormal (unsteady gait with signs of imbalance or a frank fall). Thereafter the following clinical/laboratory assessment of vestibular function was carried out with majority as per the following protocol defined by Shepard and Telian [5]:

Vestibulo-Ocular Reflex Functions (VOR)

- Occulopsia test with passive head rotation and Snellen’s chart performance (Dynamic visual acuity testing consider abnormal with resolution of letters three lines or more higher on Snellen’s chart).
- Halmagyi head thrust: repeated saccadic corrections were considered abnormal.
- Dix-Hallpike maneuver: subjective and objective positivity was considered abnormal.
- Positional nystagmus with frenzel glass: frequency and duration of nystagmus was noted.
- Rotation test with frenzel glasses: the chair was manually rotated clockwise with an angular speed of 180 degrees per second for 40 s. The nystagmus was noted soon after cessation of rotation for next 20 s. The similar procedure was undertaken with anticlockwise rotation. Presence of abnormal nystagmus on the basis of its frequency and duration was noted.
- Bithermal caloric test with frenzel glass: The EAC was alternately irrigated with warm (44°) and cold (30°) saline solution for 40 s and nystagmus recorded for next 20 s manually. A 5 min pause between the two irrigations was strictly observed. The canal paresis (CP) and directional preponderance (DP) was calculated as per frequency and duration of induced nystagmus [6].

Vestibulospinal Reflex Functions (VSR)

- Past pointing to define angular deviation as a parameter of peripheral vestibular asymmetry
- Fukuda’s test to define angular deviation as a parameter of vestibular asymmetry.
- Romberg and Tandem Romberg: to document tendency for central sway and fall
- Clinical test of Sensory Integration of Balance (CTSIB): to predict the relative influence of visual, vestibular and somatosensory cues on balance. Patient’s attempt to maintain balance is observed for 30 s in 4

Table 1 Inclusion and exclusion criteria

Inclusion criteria

1. Category II patients undergoing STM treatment as a part of ATT
2. Patients willing for a monthly follow-up and ready to participate in study protocol with strict adherence to treatment protocol
3. Age 15–60 years

Exclusion criteria

1. Patients who have received streptomycin/kanamycin earlier for any other treatment
2. Drop-outs from the study
3. Chronic ear disease: ear discharge, moderate to severe sensory-neural hearing loss
4. Mental retardation/functional patents
5. History of significant head injury or skull base fracture
6. Patients on treatment regimen other than DOTS and DOTS-plus

Table 2 Working definitions of degree of vestibulotoxicity

1. Manifest-vestibulotoxicity: Deranged VOR and/or VSR in a symptomatic patient (GRADE IV)
2. Occult vestibulotoxicity: Deranged VOR and/or VSR in asymptomatic patient (GRADE III)
3. Delayed-Manifest vestibulotoxicity will be labeled in a patient when his status from occult-vestibulotoxicity changes to Manifest-vestibulotoxicity (GRADE II)
4. No-vestibulotoxicity: No-derangement of VOR and VSR in asymptomatic patient (GRADE I)

situations viz. standing on firm surface with eyes open, standing on firm surface with eyes closed, standing on foam surface with eyes open and standing on foam surface with eyes closed. Three trials for each situation is undertaken to enable patient to maintain balance and the test is terminated as feet change position (unstable or fall). Patient's visual, somatosensory and vestibular preferences are denoted by conditions 2/4, 3/4 and 4 respectively.

A second assessment was made after 4 weeks or when self-reported with dizziness. This facilitated the creation of the 3rd category i.e. 'delayed manifest vestibulotoxicity' from the 'Occult'- or 'No- vestibulotoxicity' categories. For the symptomatic patients, an additional neurotropic drug was added (tab Neurobion) along with a short course (3–5-days) of vestibular suppressant (cinnarazine with or without antiemetic) in early course of onset to counteract the initial vestibular crisis. Thereafter necessary vestibular-balance-rehabilitation therapy was started in order to enhance vestibular compensation. The patient was counseled to continue with such rehabilitation therapy till the point of attaining dynamic compensation. Under no circumstances were the vestibular sedatives given for prolonged duration or within 5 days prior to vestibular assessment. All patients completed the standard streptomycin treatment which included 24 shots of intramuscular streptomycin 15–20 mg/kg body weight distributed over 8 weeks period (three injections per week). The follow-up was as per the

initial protocol to document the ongoing changes in each and every vestibular tests.

Statistical Analysis

Age of four (vestibulotoxicity categories) was summarized as Mean $\pm$ SD while discrete (categorical) test outcome measures in number and %. Age of four groups were compared by one way analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Tukey' post hoc test. Categorical test outcome measures were compared by Chi-square (χ^2) test. A two-sided ($\alpha = 2$) p values <0.05 ($p < 0.05$) was considered statistically significant. Analysis was performed on SPSS (Windows version 18.0, PSAW).

Observations and Results

Age matched normative data used in our laboratory from past 2 decades was used to assess the performance of each test result. The distribution of patients in vestibulotoxicity-categories I through IV were 15 (46.9 %), 9 (28.1 %), 5 (15.6 %) and 3 (9.4 %) respectively.

The age distribution of the categories showed significant difference ($p < 0.001$) in vestibular compliance (Table 3) but no effect of gender was seen. The performance of various vestibular tests as per categories are depicted in Table 4.

Table 3 Age and gender distribution

	Category I (n = 15)	Category II (n = 9)	Category III (n = 5)	Category IV (n = 3)	F/ χ^2 value	p value
Age (year)						
Mean $\pm$ SD	27.27 $\pm$ 7.10	31.44 $\pm$ 11.19	43.40 $\pm$ 10.14	50 $\pm$ 13.23	7.27	0.001
Gender						
Males	4 (26.7 %)	3 (33.3 %)	1 (20 %)	2 (66.7 %)	2.21	0.530
Females	11 (73.3 %)	6 (66.6 %)	4 (80 %)	1 (33.3 %)		

The DHI score was abnormal with onset of symptoms and clearly differentiated categories III/IV from categories I/II ($p < 0.001$). The abnormality in DHI score amongst categories III and IV was not significant though. The head shake nystagmus could not significantly differentiate the categories ($p = 0.03$) while casual gait abnormality was as effective as DHI ($p = 0.001$) in this regard. The occilopsia and head thrust tests both were again significant tools to differentiate occult vestibulotoxicity (category II) from category I ($p < 0.001$). It is worth noting that despite showing clinical significance none of the three tests viz. Casual gait, Occilopsia and Head thrust could differentiate category II from categories III/IV. Moreover (as expected) both Dix-Hallpike and Positional tests were of no significance in the entire study.

Amongst the vestibulocular tests Rotation and Bithermal-Calorics were very significant in differentiating category I from category II and category II from categories III/IV ($p < 0.001$), while Past-Pointing test was unreliable in this regard ($p = 0.23$). The spinovestibular tests viz. Fukuda's test, Romberg test, Tandem-Romberg test and CTSIB were significant in differentiating the category I from category II and category II from categories III/IV ($p < 0.001$).

An attempt was made to establish sensitivity, specificity and positive predictive value for all the tests but due to small sample size a meaningful result for individual test was not achieved. However the Occilopsia and Head-Thrust tests that showed 100 % positivity for all three categories are more likely to better predict (determine) manifest or occult-vestibulotoxicity. A larger sample is required to better define the sensitivity, specificity and positive predictive value in this regard. The overall positivity of all 12 tests combined was summated for each of the 4 categories. The all-tests-combination showed highest positivity for category IV (91.73 %) followed by III (88.3 %) and II (38.9 %). Further, the χ^2 test (after excluding category I/Dix-Hallpike/Positional tests) revealed that positivity of all-tests-combination for categories III/IV were significantly different and higher as compared to category II ($\chi^2 = 228.30$, $p < 0.001$).

Discussion

Global tuberculosis control can be regarded as one of the Millenium Development goals of WHO and accordingly RNTCP based on international recommendations had launched DOTS (Directly Observed Treatment short course) protocol in 1997. The DOTS recommends streptomycin therapy for 8 weeks in a subset that includes relapse, failures and treatment- default cases, hence much prone to AIV. Because it is possible to physiologically compensate for vestibular damage, cochleotoxicity is generally considered to be a far more serious problem [7]. Still in general, the vestibular function is much more sensitive to aminoglycosides than hearing function (except for rare mitochondrial mutations) and most vestibulotoxicity cases with preserved hearing go undiagnosed [8]. Only a few studies have reported the incidence of STM induced vestibulotoxicity (3–6 % by Dhanireddy et al. [9]) while Selimoglu et al. [10] have reported streptomycin to be the least vestibulotoxic than other aminoglycosides in animal model. The current study is first of its kind to analyze the entire range of vestibular function regarding vestibulotoxicity resulting from a 2 months course of parenteral/intramuscular streptomycin. The current evident vestibulotoxicity in Categories IV and III (Manifest and Delayed-manifest) to the tune of 25 % is much more than the reported literature while an additional 28 % of occult vestibulotoxicity (II) is a new finding. The literature on streptomycin induced vestibulotoxicity probably relates to the manifest cases only and not the occult ones (28 % in our study) which together with the manifest cases (25 %) of the present study constitute an overall incidence of 53 % (more than half) in our series. The majority of tuberculosis patients are illiterate and often phobic from treatment related morbidity leading to default unless counseled. Further larger studies need to be undertaken to reconfirm this high incidence rate. Identifying occult cases early is essential as these are likely to be future -defaulters.

The DHI being a subjective questionnaire-based assessment can be undertaken by a paramedical staff particularly in peripheral areas (in the absence of a specialist)

Table 4 Behavior of vestibular tests in different categories of vestibulotoxicities

	Category I (n = 15) (%)	Category II (n = 9) (%)	Category III (n = 5) (%)	Category IV (n = 3) (%)	χ^2 value (DF = 3)	<i>p</i> value
DHI						
Normal	15 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	32.00	<0.001
Abnormal	0 (0.0)	0 (0.0)	5 (100.0)	3 (100.0)		
Head shake nystagmus						
Normal	15 (100.0)	9 (100.0)	4 (80.0)	3 (100.0)	5.57	0.134
Abnormal	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)		
Casual gait						
Normal	15 (100.0)	1 (11.1)	0 (0.0)	0 (0.0)	28.44	<0.001
Abnormal	0 (0.0)	8 (88.9)	5 (100.0)	3 (100.0)		
Oscillopsia						
Normal	15 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	32.00	<0.001
Abnormal	0 (0.0)	9 (100.0)	5 (100.0)	3 (100.0)		
Head Thrust						
Normal	15 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	32.00	<0.001
Abnormal	0 (0.0)	9 (100.0)	5 (100.0)	3 (100.0)		
Dix-Hallpike and Positional test						
Normal	15 (100.0)	9 (100.0)	5 (100.0)	3 (100.0)	NA	NA
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Rotation test						
Normal	15 (100.0)	7 (77.8)	0 (0.0)	0 (0.0)	24.76	<0.001
Abnormal	0 (0.0)	2 (22.2)	5 (100.0)	3 (100.0)		
Bithermal caloric test						
Normal	15 (100.0)	7 (77.8)	0 (0.0)	0 (0.0)	24.76	<0.001
Abnormal	0 (0.0)	2 (22.2)	5 (100.0)	3 (100.0)		
Past pointing						
Normal	15 (100.0)	7 (77.8)	2 (40.0)	2 (66.7)	9.54	0.023
Abnormal	0 (0.0)	2 (22.2)	3 (60.0)	1 (33.3)		
Fukuda test						
Normal	15 (100.0)	5 (55.6)	1 (20.0)	0 (0.0)	18.60	<0.001
Abnormal	0 (0.0)	4 (44.4)	4 (80.0)	3 (100.0)		
Rhomberg						
Normal	15 (100.0)	8 (88.9)	0 (0.0)	0 (0.0)	27.60	<0.001
Abnormal	0 (0.0)	1 (11.1)	5 (100.0)	3 (100.0)		
Tandem Rhomberg						
Normal	15 (100.0)	6 (66.7)	0 (0.0)	0 (0.0)	23.13	<0.001
Abnormal	0 (0.0)	3 (33.3)	5 (100.0)	3 (100.0)		
Clinical tests of integration of balance (CTSIB)						
Normal	15 (100.0)	7 (77.8)	0 (0.0)	0 (0.0)	24.76	<0.001
Abnormal	0 (0.0)	2 (22.2)	5 (100.0)	3 (100.0)		

Significant *p* values <0.05 are in bold

to further enhance the overall compliance. Such tests cannot screen the occult cases but can certainly provide a degree of discomfort to suspect a case for further referral. The casual gait can distinguish the occult cases but may need a specialist to examine the gait abnormality. It was indeed surprising that even with mild gait abnormality the

occult-category patients did not complain of any symptoms. The reason may have been a good central (static) compensation not compromising the quality of life. A physical therapist trained in gait assessment can be an asset to the DOTS team. An even better option to be carried out by the paramedic is the occillopsia test with Snellen's

chart as this test has demonstrated its ability to screen all occult-vestibulotoxicity cases in the present study. The head-thrust test did show a similar performance but often needed the presence of a specialist to decipher its results. Halmagyi and Curthoys [11] have also recommended the head impulse test for early clinical diagnosis of AIV.

The absence of abnormal Dix-Hallpike and Positional testing possibly suggests a composite effect of streptomycin on central and peripheral vestibular system rather than simply dislodgment of the otoconia. The absence of Head-Shake nystagmus in manifest cases may denote a near-symmetrical severe vestibulopathy while a single case of category III may have reflected some asymmetry in evolution. Hence the use of head shake nystagmus as also pointed out by Dhanireddy et al. [9] may not be appropriate in this situation. Humphriss et al. [12] too have concluded that the head shake test is of insufficient sensitivity or specificity to be of clinical value as a screening test for. It may be possible that a good central compensation in occult-vestibulotoxicity cases would not have produced enough asymmetry to result in abnormal head-shake nystagmus. Harvey et al. [13] on the other hand have found both head shake test and head impulse test to have a low sensitivity for screening peripheral vestibular damage based on caloric test but if both are positive there is a high likelihood of a significant caloric deficit. A larger sample size may be needed to confirm the absolute inability of head shake test to detect any abnormality in contrast to what was evidenced in our small sample.

The abnormalities detected on rotation and bithermal caloric tests were similar for all the categories. None of the cases showed total absence of caloric response in this series. The incidence of absolute absence of caloric induced nystagmus is not very rare at our facility (as per the work done earlier) and the possible explanation of absence of this finding in the current study might have been that the caloric testing was done a bit early either at the onset of vestibular symptoms or before the attainment of

the status of absent vestibulo-ocular response that in turn might have been attained late after our assessment if at all. The absent calorics represent vestibular functions at lower frequency of performance while the higher frequencies are better judged with the rotation protocol. Both the frequencies of vestibular responses might have been intact when these tests were conducted. However a more precise computerized chair assessment is likely to be a better instrument to assess the different degrees of vestibulocular reflexes, which unfortunately was missed in our study owing to somewhat ‘less-objective’ chair assessment. The past pointing was randomly abnormal across all the categories indicating the unpredictable systemic effect of streptomycin on peripheral and central vestibular connections. It is yet to be established if cases with abnormal past-pointing are more likely to show delayed central compensation.

The summary of clinical tests significantly differentiating the categories of vestibulotoxicities are shown in Table 5. The Fukuda test abnormality indicated a consistent involvement of vestibulospinal system across all the categories including category II. The other vestibulospinal tests were significantly positive more for III and IV, II. The Tandem-Rhomberg test was more sensitive than the classical Romberg test to detect category II dysfunction. Hence Fukuda and Tandem-Rhomberg tests seem most appropriate for early vestibulospinal dysfunction. These 2 tests are closely followed by CTSIB test in terms of sensitivity. However a larger sample size seems more appropriate to establish such conclusions.

Apart from the small sample size, the limitations of this study are many. Firstly despite age-matched normative controls, the element of presbystasis may have influenced the overall vestibular status amongst elderly. This is well evident from Table 1 as the increasing age is more likely to have manifest vestibulotoxicity. The likelihood of vestibulotoxicity with age has also been reported by Aust [14]. Hence an elderly needs to be carefully followed up owing to other co-

Table 5 Summary of clinical tests significantly differentiating the various categories of vestibulotoxicities

Clinical tests	Cat I versus II	Cat I versus IV	Cat II versus IV	Cat II versus III	Cat I versus III + IV
Casual gait	+	+			+
Head Thrust	+	+			+
Occiplosia	+	+			+
Rotation		+	+	+	+
Bithermal caloric		+	+	+	+
Past pointing		+			+
Fukuda	+	+			+
Rhomberg		+	+	+	+
Tandem Rhomberg	+	+		+	+
m-CTSIB		+	+	+	+

morbidities (high chances of non-compliance). Secondly in absence of government approved drugs from a single source/batch (due to irregularity in National Rural Health Mission (a Govt. of India undertaking), the local-make drugs were prescribed in the present study with as many as 5–7 different pharmaceutical manufacturers. Accordingly the theoretical possibility of different pharmacokinetics/pharmacodynamics may be considered. Thirdly this study has a low degree of objectivity in the absence of electronystagmography, computerized dynamic posturography, computerized rotational chair assessment etc. Hence a great degree of subjective assessment has influenced the results of this work. Fourthly some bias must have been included owing to the subjectivity in assessment as the tests were either carried out by a trained postgraduate student/resident or confirmed from two different faculty members independently.

A study by Piloquin et al. [15] reported abnormal vestibular tests only in first month of aminoglycoside therapy while no abnormality was noted thereafter with subsequent dosage. In contrast the cochleotoxicity and nephrotoxicity worsened with prolonged treatment from 5 to 18 months. Hence to continue streptomycin for 2 months the vestibulotoxicity in particular need to be considered.

Conclusion

The onset of vestibulotoxicity needs to be registered at an early stage amongst patients undergoing streptomycin treatment for four reasons: (1) The onset of early vestibular-balance-rehabilitation-therapy may limit rapid clinical dysfunction and improves QOL; (2) An early counseling for future manifest symptoms may enhance patient's acceptance for severe dizziness translating into better compliance; (3). Other systemic toxicities such as ototoxicity and nephrotoxicity should be monitored in these subsets considering the idiosyncratic/unpredictable effect of the drug on other systems; (4) A more regular follow-up of these cases would further establish the pace of development of vestibulotoxicity in individual subjects so that those with severe morbidity may be hospitalized till completion of treatment/physical improvement. With zero non-compliance in our patients the vestibulotoxicity may not be a deciding factor for termination of streptomycin (as also suggested by Black et al. [16]) provided an in-built mechanism for patient support/counseling be incorporated in management schedule.

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Authors' Contributions MA in this Masters thesis project of his was the key person to recruit the patients from the departments of Pulmonary Medicine (with help from RG) and Internal Medicine (with help from KKS). He also conducted the basic anamnesis, otolaryngological examination, data entry and collection of references. The original idea of this work and design of study was framed by AM (corresponding author) who was the chief guide and supervisor of MA for his Masters thesis project of Otolaryngology. AM was the final authority to decide the results of vestibular examination in situations of divided opinions if any. AM was also the main person to draft the manuscript and obtaining inputs from the statistician. KKS helped in recruitment of patients from department of Internal Medicine and examining them medically. He also took the decision regarding the treatment aspects in close collaboration with RG. RG was the key person who helped in recruitment of the patients from the department of pulmonary medicine, deciding the treatment to be given and facilitating the follow up. VV, HPS, SK were instrumental in assisting AM in vestibular assessment of the patients in the department of otolaryngology as well as providing important inputs for manuscript writing as RG and KKS. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest All the authors declare that they have no conflict of interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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